Resistant congestion syndrome - my patient also has hyponatremia, what should I do?

Amina Rakisheva

10.06.2023
WHAT SHOULD I DO?
### Diuretics

**NYHA class II-IV heart failure with reduced ejection fraction (LVEF ≤40%) (1)**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics are recommended in patients with HFrEF with signs and/or symptoms of congestion to alleviate HF symptoms, improve exercise capacity, and reduce HF hospitalizations.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>

**Pharmacological treatments to be considered in patients with (NYHA class II-IV) heart failure with mildly reduced ejection fraction**

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<td>Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs.</td>
<td>I</td>
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**Recommendations for the initial treatment of acute heart failure (2)**

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<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
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<tr>
<td>Diuretics</td>
<td></td>
<td></td>
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<tr>
<td>Intravenous loop diuretics are recommended for all patients with AHF admitted with signs/symptoms of fluid overload to improve symptoms.</td>
<td>I</td>
<td>C</td>
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The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology

Wilfried Mullens1,2,*, Kevin Damman3, Veli-Pekka Harjola4, Alexandre Mebazaa5, Hans-Peter Brunner-La Rocca6, Pieter Martens1,2, Jeffrey M. Testani7, W.H. Wilson Tang8, Francesco Orso9, Patrick Rossignol10, Marco Metra11, Gerasimos Filippatos12,13, Petar M. Skuli14, and Andrew J. Coats16

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comparator</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-sided</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JVP &gt; 8 cm</td>
<td>48%</td>
<td>78%</td>
<td>RAP &gt; 7 mmHg</td>
<td>Difficult in obese patients</td>
</tr>
<tr>
<td>Jugular venous reflux</td>
<td>50%</td>
<td>75%</td>
<td>RAP &gt; 7 mmHg</td>
<td>Difficult in obese patients</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>51%</td>
<td>62%</td>
<td>RAP &gt; 7 mmHg</td>
<td>Difficult in obese patient, non-HF causes</td>
</tr>
<tr>
<td>Bilateral leg oedema</td>
<td>94%</td>
<td>10%</td>
<td>RAP &gt; 7 mmHg</td>
<td>Non-HF oedema gives false positive</td>
</tr>
<tr>
<td>Left-sided</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>50%</td>
<td>73%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>Multiple reasons for dyspnoea</td>
</tr>
<tr>
<td>Dyspnoea on exertion</td>
<td>64%</td>
<td>52%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>Multiple reasons for dyspnoea on exertion</td>
</tr>
<tr>
<td>Orthopnoea</td>
<td>66%</td>
<td>47%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>May be non-cardiac in origin or absent</td>
</tr>
<tr>
<td>S3</td>
<td>73%</td>
<td>42%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>Intra-observer variability</td>
</tr>
<tr>
<td>Rales</td>
<td>13%</td>
<td>90%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>May be non-cardiac in origin or absent</td>
</tr>
<tr>
<td><strong>Echo-cardiographic evaluation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-sided</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collapse (&lt; 50%) IVC</td>
<td>12%</td>
<td>27%</td>
<td>RAP &gt; 7 mmHg</td>
<td>Difficult to use in positive pressure ventilated patients</td>
</tr>
<tr>
<td>Inspiratory diameter IVC &lt; 12 mm</td>
<td>67%</td>
<td>91%</td>
<td>RAP &gt; 7 mmHg</td>
<td>Cannot be used in positive pressure ventilated patients</td>
</tr>
<tr>
<td>Left-sided</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral inflow E-wave velocity &gt; 50 (cm/s)</td>
<td>92%</td>
<td>28%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>Difficult when fusion of E and A wave</td>
</tr>
<tr>
<td>Lateral E/e’ &gt; 12</td>
<td>64%</td>
<td>53%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>Less accurate in advanced heart failure and CRT</td>
</tr>
<tr>
<td>Deceleration time &lt; 130 ms</td>
<td>81%</td>
<td>80%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>Difficult when fusion of E and A wave</td>
</tr>
<tr>
<td>Pulmonary vein S/D &lt; 1</td>
<td>83%</td>
<td>72%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>Intra-observer variability in Doppler measurements of the vein</td>
</tr>
<tr>
<td>Diffuse B-lines on lung ultrasound*</td>
<td>85.7%</td>
<td>40%</td>
<td>PCWP &gt; 18 mmHg</td>
<td>B-lines might be present in non-cardiac conditions</td>
</tr>
</tbody>
</table>
The use of diuretics in heart failure with congestion — a position statement from the Heart Failure Association of the European Society of Cardiology

Wilfrid Mullens\textsuperscript{1,2}, Kevin Dammann\textsuperscript{1}, Hans-Peter Brunner-La Rocca\textsuperscript{6}, Pierre W.H. Wilson Tang\textsuperscript{8}, Francesco Orsolic\textsuperscript{6}, Gerasimos Filippatos\textsuperscript{12,13}, Petar M. Vuckovic\textsuperscript{2}, and Andrew J. Coats\textsuperscript{16}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Orthopnea</th>
<th>JVP (cm)</th>
<th>Hepatomegaly</th>
<th>Edema</th>
<th>6MWT</th>
<th>NP (one of both): BNP -NT-proBNP</th>
<th>Chest X-ray</th>
<th>Vena Cava imaging (16)</th>
<th>Lung Ultrasound (22)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None</td>
<td>&lt;8 and no HJR</td>
<td>Absent</td>
<td>None</td>
<td>&gt;400m</td>
<td>&lt;100 -400*</td>
<td>clear</td>
<td>none of two: - Max diameter &gt;2.2 cm - collapsibility &lt;50%</td>
<td>&lt;15 B-lines when scanning 28-sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;8</td>
<td>Liver edge</td>
<td></td>
<td>300-400m</td>
<td>100-299</td>
<td>clear</td>
<td>One of two: - Max diameter &gt;2.2 cm - collapsibility &lt;50%</td>
<td>15-30 B-lines when scanning 28-sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8-10 or HJR+</td>
<td>Moderate pulsatile enlargement</td>
<td>+1</td>
<td>200-300m</td>
<td>400-1500</td>
<td>cardiomegaly</td>
<td>- pulmonary venous congestion* - small pleural effusions*</td>
<td>&gt;30 B-lines when scanning 28-sites</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11-15</td>
<td>Massive enlargement and tender</td>
<td>+2</td>
<td>100-200m</td>
<td>1500-3000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;16</td>
<td></td>
<td>+3/+4</td>
<td>&lt;100m</td>
<td>&gt;500</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CONGESTED**

**EUVOLEMA**

![Diagram](image-url)
Diuretics: first 24 hours
Diuretics: first 24 hours
Diuretics: first 24 hours
Diuretics: first 24 hours
Diuretics: second day

Second day of admission
- Evaluate 24-hour urine output
  - UO < 3-4 L: Double-loop diuretic dose until maximal loop diuretic dose
  - UO > 3-4 L: Continue current dose until decongestion

Persistent congestion
- Assess within 6 hours
  - < 100 mL/hour diuresis: UO < 3-4 L
    - No maximal loop diuretic dose?
      - Yes: Combinational diuretic therapy
        - First line: thiazides
        - Second line: Acetazolamide or amiloride
        - Third line: consider SGLT2-I dose according to table 2
      - No: Consider discharge
    - Yes: Repeat until maximal loop diuretic dose
- UO > 3-4 L

Parallel interventions

Parallel evaluation
- Consider reducing loop diuretic dose if daily UO > 3 L.
Diuretic therapy

1. Blocks carbonic anhydrase
   \[\text{\(\text{NaHCO}_3\) excretion}\]
2. Osmotic diuretic
   \[\text{\(\text{H}_2\text{O}\) excretion}\]
3. Blocks sodium-potassium-chloride cotransporter
   \[\text{\(\text{Na}\) excretion}\]
   \[\text{\(\text{K}\) excretion}\]
   \[\text{\(\text{Cl}\) excretion}\]
4. Blocks sodium-chloride transporter
   \[\text{\(\text{NaCl}\) excretion}\]
5. Antagonises aldosterone receptor
   \[\text{\(\text{Na}\) excretion}\]
   \[\text{\(\text{K}\) retention}\]
Diuretics: mechanism of diuretics resistance

Pathophysiology

- ↓ CO
- ↑ CVP
- ↓ Plasma albumin
- ↓ RBF and GFR
- ↑ RAAS and SNS

Mechanisms of loop diuretic resistance

- Reduced absorption of loop diuretic
- Unable to bind to albumin
- Reduced filtration
- Proximal Na reabsorption
- Organic acids like blood urea nitrogen competitively bind to OAT, reducing diuretic availability in the tubule
- Filtered albumin binds to furosemide, reducing availability at cotransporter
- Distal Na reabsorption

Hyponatremia
Background

• Approximately 20-30% of HF classes III-IV have hyponatremia

• It is associated with increased risk of death, independent of other comorbidities

• Hyponatraemic patients with HF demonstrate more severe congestive symptoms with worse diuretic response and might present with neurological manifestations, from subtle cognitive impairment to life-threatening symptoms in severe or rapid-onset hyponatraemia

• Even mild hyponatremia among with ADHF, regardless of LVEF, is associated with increased in-hospital and post-discharged mortality, prolonged hospital length of stay and frequent hospitalization
Relationship between admission serum sodium concentration and clinical outcomes in patients hospitalized for heart failure: an analysis from the OPTIMIZE-HF registry

Mihai Gheorghiade, William T. Abraham, Nancy M. Albert, Wen Barry H. Greenberg, Christopher M. O’Connor, Lilin She, Clyde and Gregg C. Fonarow on behalf of the OPTIMIZE-HF Investigators.
### Potential causes and factors in heart failure

#### Dilutional
- Elevated AVP due to reduced cardiac output in advanced heart failure.
- SIADH, including drug-induced SIADH, most commonly due to antidepressants, antipsychotic agents, anticonvulsants, cytotoxic agents and pain medications (rare reports of SIADH in the course of amiodarone or ACEi therapy).
- Adrenal insufficiency, hypothyroidism (due to elevated AVP).
- Advanced kidney disease.
- Liver cirrhosis.

#### Depletional
- Low sodium intake (salt-restricted diet).
- Intensive diuretic treatment (combination therapy, high doses of diuretics).
- Acute gastrointestinal losses (diarrhoea, vomiting).
- Third-space losses (ascites, intestinal obstruction).
- Flecainide—sodium channel blocker (rare reports of hyponatraemia, probably due to inhibition of sodium reabsorption in the distal nephron).
- Potassium and/or magnesium deficiency (extracellular sodium depletion due to a shift of sodium into the intracellular compartment).
- Severe hyperglycaemia (hypovolaemic hyponatraemia due to glucosuria-induced osmotic diuresis*).

#### Pseudohyponatremia
- Severe hyperglycaemia.
- Hyperosmolar radioccontrast media.
- Hypertriglyceridaemia, hypercholesterolaemia.
- Monoclonal gammopathies.
Classification

Hyponatremia

- Hyperosmotic
- Isosmotic
- Hypoosmotic

- Hypervolemic
- Euvolemic
- Hypovolemic

mild 130-135 mmol/L
moderate 125-129 mmol/L
profound <125 mmol/L
Plasma osmolality

- are primarily determine by changes in serum concentration of sodium in its associated anions
- normal value 285-295 mOsm/L

- Total osmolality is defined as the concentration of all solutes in a given weight water, regardless of whether or not the osmoles can move across biological membranes

- Effective osmolality (tonicity) refers to the number of osmoles that contribute water movement between the intracellular and extracellular compartment

- Formula: 2 Na (mmol/L) + 2 K (mmol/L) + urea (mmol/L) + glucose (mmol/L) + 0.033 protein (g/L)
Effects of AVP in the Nephron

V1aR:
- Myocardium
- Vascular smooth muscle
- Hepatocytes
- Glycogenolysis
- Uterine contractions

V1bR and V3R:
- Anterior pituitary gland
- Release of ACTH

V2R:
- Vascular endothelium and smooth muscle
- Kidneys (collecting tubules)
- Vasodilatation
- Release of von Willebrand Factor
- Release of Factor VIII
- Water reabsorption

Ferbrugge et al. https://doi.org/10.1016/j.jacc.2014.12.010
Non-osmotic and osmotic pathways of AVP release

AVP secretion is modulated by both osmotic and non-osmotic pathways.

In the osmotic pathway, an increase in plasma osmolality stimulates increased production of AVP in the hypothalamus. In the non-osmotic pathway, decreases in arterial blood pressure and circulatory blood volume diminish the sensitivity of baroreceptors, resulting in AVP release even at a lower serum osmolality.
Symptoms of hyponatremia

**Neurological symptoms**
- High levels of extracellular glutamate in the brain → impairing mitochondrial distribution and decrease in adenosine triphosphate

**Osteoporosis**
- Stimulation of osteoclastogenesis and increased osteoclastic resorption
  - Reduced vitamin D levels
  - Lower activity of sodium-dependent vitamin C transporter → oxidative stress

**Skeletal sarcopenia**

**Cardiac fibrosis**
- Interstitial and perivascular collagen deposits
  - Decreased cell division → loss of cardiac myocyte number
Diagnostic algorithm in HF associated hyponatremia

1. **HYponatremia** (serum sodium <135 mEq/L)
   - Assess plasma osmolality

2. **Low** (<285 mOsm/L)
   - **ISOTONIC HYponatremia**
     - Hyperlipidemia
     - Hyperproteinemia
   - **HYPOTONIC HYponatremia**
     - Assess volume status-evaluation of vital signs, jugular venous pressure, skin turgor, peripheral edema

3. **High** (>295 mOsm/L)
   - **HYPERTONIC HYponatremia**
     - Hyperglycemia
     - Radiocontrast media
     - Mannitol
     - Ethanol
     - Methanol

4. **DEPLETIONAL HYponatremia**
   - Hypovolemia
   - Urinary osmolality <100 mOsm/L

5. **DILUTIONAL HYponatremia**
   - Hypervolemia
   - Urinary osmolality ≥100 mOsm/L

*J. Pers. Med. 2023, 13(1), 140*
Algorithm for the hyponatremia management

**Hyponatremia** (serum sodium concentration <135 mmol/L) in HF pts

Stopping/reducing distally working diuretics (thiazide-type diuretics; withhold MRA only temporarily and only in severe hyponatremia; reinstitute MRA immediately after improvement)

Correction of K⁺ and Mg²⁺ deficiencies

**Dilutional hyponatremia**
- Clinical presentation: hypervolemia
- Urinary osmolality ≥100 mOsm/L

1) Limited water intake
2) Loop diuretics
   - Consider addition of SGLT2i to loop diuretics
   - Consider addition of acetazolamide
3) Adequate treatment of HF (to increase cardiac output):
   - In severe ADHF: consider inotropes and/or vasodilators
   - In other HF pts: ACEi or ARNI
4) In congested ADHF pts with refractory hyponatremia consider:
   - Vasopressin antagonists
   - Hypertonic saline with high-dose loop diuretics

**Depletional hyponatremia**
- Clinical presentation: hypovolemia
- Urinary osmolality <100 mOsm/L

1) Mild hyponatremia:
   - oral sodium and water restitution
   - pts education (balanced diet, adequate fluid intake)
2) More severe hyponatremia: intravenous saline solution
   (isotonic or hypertonic depending on volume status and severity of hyponatremia)
   - If no severe hyponatremia symptoms are present, the rate of correction of sodium concentration should be <5 mmol/L per day
   - If serum sodium concentration is <125 mmol/L, the rate of correction may be up to 10 mmol/L per day
   - Do not exceed the rate of correction of sodium concentration of 10 mmol/L per day due to the risk of pontine myelinolysis
### Management of dilutional hyponatraemia in HF

<table>
<thead>
<tr>
<th>Known and potential mechanisms</th>
<th>Drug</th>
</tr>
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<tbody>
<tr>
<td>Reduced AVP secretion</td>
<td></td>
</tr>
<tr>
<td>➤ Indirect effect through immediate improvement of cardiac output.</td>
<td>➤ Inotropes.</td>
</tr>
<tr>
<td>➤ Indirect effect through reverse cardiac remodelling and subsequent improvement of cardiac output.</td>
<td>➤ Vasodilators.</td>
</tr>
<tr>
<td>➤ Direct inhibition of AVP release.</td>
<td>➤ Dual AVP antagonists.</td>
</tr>
<tr>
<td>Antagonising AVP effects in the collecting ducts</td>
<td>➤ ACEi.</td>
</tr>
<tr>
<td></td>
<td>➤ ARNI.</td>
</tr>
<tr>
<td></td>
<td>➤ SGLT2 inhibitors.</td>
</tr>
<tr>
<td></td>
<td>➤ Dual and selective V2 receptor AVP antagonists.</td>
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Management of dilutional hyponatraemia in HF

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<tr>
<td>Reduced AVP secretion</td>
<td><img src="image1.png" alt="Increased proximal (but not distal) sodium excretion." /></td>
</tr>
<tr>
<td></td>
<td><img src="image3.png" alt="Other mechanisms increasing sodium delivery to the Henle’s loop and distal nephron." /></td>
</tr>
<tr>
<td></td>
<td><img src="image5.png" alt="Improved renal blood flow through afferent arterioles (increased glomerular filtration)." /></td>
</tr>
<tr>
<td>Antagonising AVP effects in the tubule</td>
<td><img src="image7.png" alt="Increased proximal (but not distal) sodium excretion." /></td>
</tr>
</tbody>
</table>

*Image descriptions and specific drug names have been added for clarity.*
Management of dilutional hyponatraemia in HF

**Known and potential mechanisms**

- **Reduced AVP secretion**
  - Indirect effect through immediate improvement of cardiac output.

- **Antagonising AVP effects in the distal nephron**
  - Preservation of the urine-diluting properties of the distal nephron by increasing distal nephron flow.

**Drug**

- **Inotropes.**
- **Vasodilators.**
- **Dual AVP antagonists.**

- **Loop diuretics.**
- **Acetazolamide.**
- **SGLT2 inhibitors.**
- **Hypertonic saline solution.**

**Other mechanisms increasing sodium delivery to the Henle’s loop**

- **Reduced osmotic gradient of the renal medulla (reduced driving force for AVP-dependent free water reabsorption)**
  - Improved renal blood flow through the vasa recta (increased ‘washout’).
  - Decreased sodium reabsorption in the Henle’s loop.
  - Decreased urea reabsorption in the collecting ducts.

**Osmotic diuresis**

- **SGLT2 inhibitors.**
- **Hypertonic saline solution.**